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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,669	05/25/2000	Kenneth H. Grabstein	2831-E	7760

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IMMUNEX CORPORATION
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EXAMINER

NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 05/20/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/578,669

Applicant(s)
Grabstein et al

Examiner
Mark Navarro

Art Unit
1645



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-63 is/are pending in the application.
- 4a) Of the above, claim(s) 30-34, 39, 45, and 47-63 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-29, 35-38, 40-44, and 46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

Art Unit: 1645

DETAILED ACTION

Applicants amendment filed February 24, 2003 (Paper Number 12) has been received and entered.

Election/Restriction

Applicants are again arguing that the claims have been improperly restricted. Applicants assert that MPEP 803.02, citing *In re Harnisch*, it is improper for the PTO to refuse examination that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. Unity of invention can be determined in a two-step test; first, whether the alternative members share a common utility; second, whether they share a substantial structure essential to that utility. Applicants assert that the claims share a common utility and a structural feature. Applicants arguments have been fully considered but are not found to be persuasive.

Applicants arguments are not found to be persuasive in view of the term "MUTEIN." Dorlands Medical Dictionary, 27th Edition, 1988, defines "mutein" as "arising as a result of a mutation; it is analogous to the wild-type protein but does **not necessarily have** the same enzymological, immunological or physicochemical properties." (Emphasis added). Consequently, the substantial structure feature is lacking, the amount of mutation that may be present and still be considered a mutein is not set forth, and is deemed to be open ended. Furthermore, as set forth in MPEP 803.04 molecules with a distinct structure are separate and distinct inventions. Applicants

Art Unit: 1645

are reminded that sickle cell anemia involves a single amino acid substitution of valine for glutamate. Accordingly, muteins are deemed distinct molecules from the wild type IL-15, and this restriction is still maintained.

It is noted that claim 42 properly belongs to Group I, and has been included along with the rest of Group I.

Accordingly, claims 26-63 are pending in the instant application, of which claims 30-34, 39, 45, and 47-63 are withdrawn from further consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

1. The rejection of claims 26-27, 35-38, 40-41, 43 and 46 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, ~~if the differences between the subject matter sought to be patented and the prior art are~~ such that the subject matter as a whole would have been obvious at the time the invention was made to a person

Art Unit: 1645

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. The rejection of claims 26-29, 35-38, 40-44 and 46 under 35 U.S.C. 103(a) as being unpatentable over Giri *et al* and Grabstein *et al* in view of Ferrara *et al* and Hakimi *et al* is maintained.

Applicants are asserting that both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicant's further assert that Giri neither teaches nor suggests an IL-15 antagonist. Applicants further assert that even assuming arguendo that Grabstein may teach or suggest making IL-15 antagonist, Grabstein does not teach or suggest the antagonists as claimed, which comprises an IL-15 conjugated to a chemical group that interferes

Art Unit: 1645

with the ability of IL-15 to transduce through the IL-15 receptor complex. Applicants finally assert that Hakimi does not teach or even suggest to conjugate IL-15 to PEG as the Examiner characterizes the reference in the "motivation" statement.

Applicants arguments have been fully considered but are not found to be fully persuasive.

First, the Examiner has relied only upon the teachings of Giri et al, Grabstein et al, Ferrara et al, and Hakimi et al for both suggestion and reasonable expectation.

Second, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed Cir. 1986).

Third, Applicants further assert that even assuming arguendo that Grabstein may teach or suggest making IL-15 antagonist, Grabstein does not teach or suggest the antagonists as claimed, which comprises an IL-15 conjugated to a chemical group that interferes with the ability of IL-15 to transduce through the IL-15 receptor complex. However, as taught by the combination of references this molecule is readily apparent. Giri teaches of IL-15 and that it has shared bioactivities with IL-2. Ferrara et al teach that severity of GVHD was reduced in patients in which IL-2 was inhibited. Clearly, one of ordinary skill in the art would be motivated to inhibit the activity of IL-15 in patients with GVHD, given that inhibiting IL-2 has been shown to work, and that IL-15 and IL-2 have shared bioactivities. Obviousness does not require absolute predictability but only a reasonable expectation of success. See In re Merck and Company Inc.

Art Unit: 1645

800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Circ. 1988).

Finally, Applicants assert that Hakimi does not teach or even suggest to conjugate IL-15 to PEG as the Examiner characterizes the reference in the "motivation" statement. However, Applicants apparently have not understood the motivational statement. Hakimi et al teaches that proteins conjugated with PEG result in a substantial loss of protein binding to its receptor. This is the "motivational statement" to attach PEG to IL-15 (IL-15 having been taught by Giri et al) to generate an antagonist of IL-15. Applicants further assert that the Examiner appears to have examined a process for making an IL-15 antagonist, not the product *per se*. Applicants are reassured that the product, *per se*, was examined, and found to be obvious. Since IL-15-PEG fusions do not occur naturally, the product, *per se*, must first be produced.

The claims are directed to an antagonist of interleukin 15 activity comprising IL-15 conjugated with a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex.

Giri et al (The EMBO Journal Vol. 13 (12), pp 2822-2830, 1994) teach of the cytokine IL-15 having shared bioactivities with IL-2. Giri *et al* further teach that analysis of IL-15 interaction with subunits of the IL-2 receptor revealed that the α subunit was not involved in IL-

Art Unit: 1645

IL-15 binding. Giri *et al* further set forth that both the β and γ chains are required for IL-15 binding and signaling. (See abstract).

Grabstein *et al* (Science Vol. 264, pp 965-968, May 13, 1994) teach that monoclonal antibodies to the β -chain of the IL-2 receptor inhibited the biological activity of IL-15. (See abstract).

Neither Giri *et al* nor Grabstein *et al* teach of an antagonist of IL-15 comprising IL-15 conjugated with a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex.

Ferrara *et al* (Journal of Immunology Vol. 137 (6), pp 1874-1877, Sept 15, 1986) teach that the severity of GVHD was reduced by both clinical and histologic parameters when transplant recipients received injections of a monoclonal antibody directed against the interleukin 2 receptor. (See abstract)

Hakimi *et al* (U.S. Patent Number 5,539,063) teach that when proteins are conjugated with PEG it results in a substantial loss of protein binding to its receptor. (See column 17).

Given that 1) Giri *et al* and Grabstein *et al* have taught of the interleukin 15 molecule and its biologically shared bioactivities with IL-2, and that Ferrara *et al* have taught of reducing the severity of GVHD by inhibiting the activity of IL-2, and that Hakimi *et al* has taught that proteins conjugated to PEG result in a substantial loss of protein activity, it would have been *prima facie*

Art Unit: 1645

obvious to have taken the IL-15 as taught by Giri et al or Grabstein et al and to have conjugated the IL-15 to PEG as taught by Hakimi et al to create an antagonist of IL-15 activity. One of skill in the art would have been motivated to create such an antagonist in view of the teaching by Ferrara et al that GVHD severity was reduced by inhibiting the activity of IL-2 and the teaching by Giri et al that IL-15 has shared bioactivities with IL-2.

For reasons of record in Paper Number 11, as well as the reasons set forth above, this rejection is maintained.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Art Unit: 1645

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should be faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.



Mark Navarro

Primary Examiner

May 14, 2003
